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Hyponatremia in the Dialysis Population



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Sodium derangements are among the most frequently encountered electrolyte disorders in patients with end-stage renal disease. As dialysis patients are predisposed to hyponatremia via multiple pathways, assessment of extracellular volume status is an essential first step in disentangling potential etiologic factors. In addition, multiple large population-based studies indicate that proxies of malnutrition (e.g., low body mass index, serum albumin, and serum creatinine levels) and loss of residual kidney function are important determinants of hyponatremia in dialysis patients. Among hemodialysis and peritoneal dialysis patients, evidence suggests that incrementally lower sodium levels are associated with increasingly higher death risk, highlighting the long-term risk of hyponatremia. Whereas in conventional survival models incrementally lower serum sodium concentrations are associated with worse mortality in hemodialysis patients, studies that have examined repeated measures of predialysis sodium have demonstrated mixed associations of time-varying sodium with higher mortality risk (i.e., U-shaped vs. inverse linear relationships). Although the causality of the hyponatremia-mortality association in dialysis patients remains uncertain, there are several plausible pathways by which lower sodium levels may lead to higher death risk, including central nervous system toxicity, falls and fractures, infection-related complications, and impaired cardiac function. Areas of uncertainty ripe for future studies include the following: (i) mechanistic pathways by which lower serum sodium levels are linked with higher mortality in dialysis patients, (ii) whether correction of sodium derangements improves outcomes, (iii) the optimal sodium target, and (iv) the impact of age and other sociodemographic factors on hyponatremia-outcome associations.

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KEYWORDS: hemodialysis; hyponatremia; mortality risk; peritoneal dialysis; survival model; sodium

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Hyponatremia is among the most common electrolyte disorders in dialysis patients.^{1–3} Although prevalence estimates vary depending on the criteria used for the definition of hyponatremia and underlying study population characteristics (e.g., incident vs. prevalent dialysis patients, dialysis modality), epidemiologic data suggest that approximately 6% to 29% of hemodialysis^{3–8} and 11% to 26% of peritoneal dialysis patients^{2,9–14} have serum sodium levels ≤ 135 mEq/l (Table 1), which is substantially higher than that of the general population. However, despite the frequent occurrence of sodium derangements in dialysis patients, there remain substantial knowledge gaps regarding its prognostic implications and management in this population. Indeed, a growing body of evidence

suggests that hyponatremia is a risk factor for mortality as well as substantial morbidity, including central nervous system toxicity,^{15–17} hip fracture,¹⁸ immune dysfunction and infection,^{14,19–21} and cardiovascular complications.^{22,23} In this review, we examine the pathophysiology of serum sodium derangements in dialysis patients; review epidemiologic data of correlates of hyponatremia; summarize existing studies of hyponatremia and mortality, including underlying mechanisms and optimal sodium targets; and outline potential management strategies for dysnatremia in hemodialysis and peritoneal dialysis patients.

Pathophysiology of Hyponatremia in Dialysis Patients

Patients with end-stage renal disease are uniquely predisposed to hyponatremia, and a number of shared and distinct risk factors may be contributory among those receiving hemodialysis versus peritoneal dialysis. One framework for disentangling potential causes of hyponatremia is to consider accompanying changes in extracellular volume (ECV) status (Figure 1).^{24,25} First, if

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Table 1. Prevalence and incidence of low serum sodium levels in selected hemodialysis (HD) and peritoneal dialysis (PD) cohorts

HD patients			
Author (year)	Study population	Definition	Incidence/prevalence
Waikar <i>et al.</i> (2011) ⁸	1549 prevalent HD patients from HEMO trial (US)	Lowest quartile (Sodium ≤ 136 mEq/l)	Prevalence: 29%
Hecking <i>et al.</i> (2012) ⁵	11,555 prevalent HD patients (DOPPS I & III)	Mean sodium < 135 mEq/l	Prevalence: 10%
Sahin <i>et al.</i> (2012) ⁷	697 prevalent HD patients (Turkey)	Sodium < 135 mEq/l	Prevalence: 6%
Nigwekar <i>et al.</i> (2012) ⁶	6127 incident HD patients (US – ArMORR)	Sodium < 135 mEq/l	Prevalence: 13%
Dekker <i>et al.</i> (2016) ⁴	8883 HD patients (Europe – MONDO)	Sodium < 135 mEq/l	Prevalence: 13%
Rhee <i>et al.</i> (2016) ³	27,180 incident HD patients (US)	Sodium < 134 mEq/l	Prevalence: 8%
PD patients			
Author (year)	Study population	Definition	Incidence/prevalence
Dimitriadis <i>et al.</i> (2014) ¹¹	198 PD patients (Canada)	Sodium < 130 mmol/l	Incidence: 15%
Kang <i>et al.</i> (2013) ¹²	387 PD patients (Korea)	Sodium < 135 mmol/l	Incidence: 75%
Chen <i>et al.</i> (2014) ¹⁰	318 incident/prevalent PD patients (Taiwan)	Sodium ≤ 135 mEq/l	Prevalence: 26%
Chang <i>et al.</i> (2014) ⁹	441 incident PD patients (Korea)	Sodium < 135 mEq/l	Prevalence: 13%
Tseng <i>et al.</i> (2014) ¹³	99 PD patients admitted for peritonitis (China)	Sodium ≤ 130 mEq/l (2 occasions)	Prevalence: 27%
Xu <i>et al.</i> (2015) ⁴⁸	476 incident/prevalent PD patients (China)	Sodium ≤ 135 mmol/l	Prevalence: 11%
Ravel <i>et al.</i> (2016) ²	4687 incident PD patients (US)	Sodium < 136 mEq/l	Prevalence: 9%

ArMORR, Accelerated Mortality on Renal Replacement; DOPPS, Dialysis Outcomes and Practice Patterns; HD, hemodialysis; HEMO, Hemodialysis; MONDO, MONitoring Dialysis Outcomes; PD, peritoneal dialysis.

hyponatremia is accompanied by (i) an *increase in ECV* or weight, this suggests that a gain in electrolyte-free water is the basis for the sodium derangement, and may be a consequence of increased free water intake, and potentially excess sodium intake relative to the capacity for excretion although not to the same degree as free water. In the presence of excess free water intake, hyponatremia may be further exacerbated by dysregulation of thirst, loss of residual kidney function, or inadequate ultrafiltration. Although there are fluctuations in hemodialysis patients' ECV status over the course of the inter-dialytic interval, it is likely that a large proportion of observed hyponatremia cases are those of increased ECV status, given their tendency toward free water accumulation and routine laboratory testing before hemodialysis (i.e., predialysis serum sodium measurement).

In contrast, if there is (ii) *no change in ECV status*, the differential diagnosis of hyponatremia includes a gain of osmotically active solutes restricted to the extracellular fluid compartment (e.g., glucose, paraproteins). In terms of the former, in patients with severe hyperglycemia, elevated glucose levels increase serum tonicity, leading to a shift of electrolyte-free water from the intracellular to extracellular fluid compartments and subsequent hyponatremia.²⁴ In addition, in the context of kidney dysfunction, infusion of exogenous solutes (e.g., mannitol; immune globulin suspended in mannitol, maltose, or sucrose; glycine, sorbitol, or mannitol-based surgical irrigation solutions) will also result in extracellular fluid compartment solute retention, electrolyte-free water shifts, and isotonic or hypertonic hyponatremia.^{24,26–28} With respect to the latter, with certain analytic methods presence of hyperlipidemia and hyperproteinemia may lead to pseudohyponatremia, a

laboratory artifact, in which the sodium concentration in the water portion of plasma is not *per se* altered but the sodium concentration per unit of plasma is reduced.²⁹ Alternatively, loss of intracellular solutes (e.g., potassium, inorganic phosphate) due to protein-energy wasting may lead to a compensatory shift of sodium from the extracellular to intracellular fluid compartments; in the absence of residual kidney function or in the presence of vasopressin, electrolyte-free water will remain in the body, and a large proportion will distribute to the extracellular fluid compartment, leading to hyponatremia.²⁴ Indeed, rigorous examination of several well-described hemodialysis and peritoneal dialysis cohorts have observed that indices of malnutrition (e.g., low lean tissue mass, decreased body weight, lower serum creatinine as a proxy of muscle mass) were potent predictors of hyponatremia,^{4,8,11} and it has been hypothesized that this may be related to inadequate sodium consumption relative to free water intake,⁴ low potassium intake,¹¹ and catabolism of intracellular inorganic phosphates.^{4,24}

Notably in peritoneal dialysis patients, the osmotically active molecules of icodextrin solution metabolites (e.g., maltose, maltotriose, other glucose multimers) may also lead to decrements in serum sodium levels via a dilutional effect.³⁰ Although only a fraction of icodextrin is absorbed, the portion that is absorbed is converted to oligosaccharides and maltose, and further metabolism is prevented by absence of circulating maltase.³¹ Previous studies have observed that, over the course of an icodextrin exchange, sodium levels acutely decline with initiation, stabilize over time, then return to baseline levels following completion of the exchange; small increases in tonicity with icodextrin also may be observed.^{30,32} Although icodextrin-related sodium

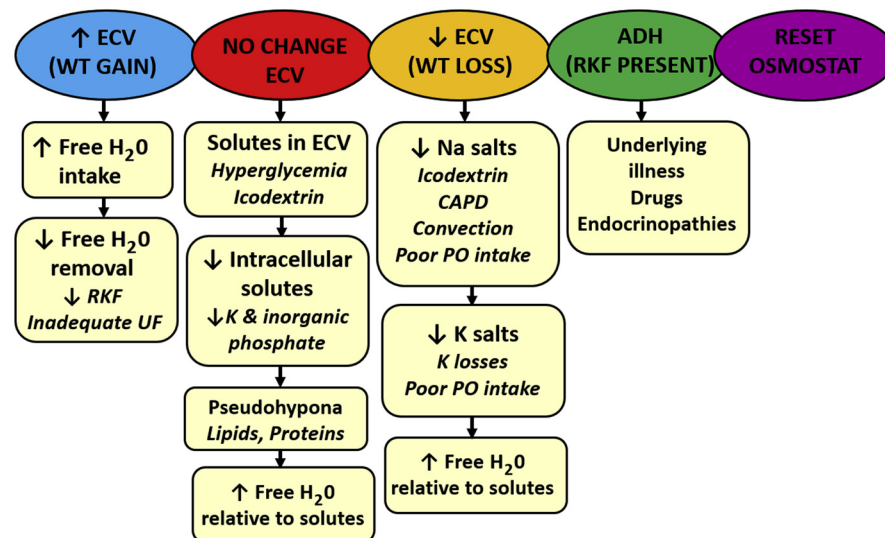


Figure 1. Risk factors for hyponatremia in dialysis patients. Upward-pointing arrow = increased; downward-pointing arrow = decreased. ADH, antidiuretic hormone; CAPD, continuous ambulatory peritoneal dialysis; ECV, extracellular volume; H₂O, water; K, potassium; PO, oral; RKF, residual kidney function; UF, ultrafiltration; WT, weight.

changes are typically mild, there have been case reports of adverse neurologic events (e.g., seizures) in the context of severe hyponatremia ensuing from icodextrin treatment in the presence of other hyponatremia-related risk factors (i.e., hyperglycemia from underlying diabetes).³³

Although infrequently observed in the dialysis population, if hyponatremia is accompanied by (iii) an *ECV deficit*, this may be due to a loss of sodium and potassium salts resulting from poor nutritional intake or excess losses (e.g., gastrointestinal, peritoneal dialysate). Although hyponatremia in peritoneal dialysis patients is predominantly related to sodium and free water retention (i.e., resulting in increased ECV status) and accumulation of osmotically active icodextrin metabolites (i.e., resulting in unchanged ECV status), length of the dwell time may have some impact on the relative removal of sodium versus water and subsequent serum sodium levels.^{2,11,34} Although “small pores” remove both sodium and water, “aquaporins” remove water only. Given that ultrafiltration largely occurs via aquaporins versus small pores during early versus later phases of the dwell, respectively, long dwell times observed with continuous ambulatory peritoneal dialysis (in contrast to more rapid-cycling automated peritoneal dialysis) may result in greater sodium removal. Furthermore, long day dwells using icodextrin will result in greater sodium removal due to increased ultrafiltration occurring via small pores.³⁵ Finally, although partial nephrogenic diabetes insipidus and impaired urinary concentration are typically characteristic of advanced chronic kidney disease,³⁶ in dialysis patients with substantial residual kidney function, inadequate vasopressin suppression leading

to free water excess, as well as change in the set point for serum sodium may be contributory.^{24,25}

Correlates of Hyponatremia in Dialysis Patients Hemodialysis Patients

A number of epidemiologic studies have sought to identify clinical characteristics associated with hyponatremia in the hemodialysis population. In a secondary analysis of 1549 prevalent hemodialysis patients from the Hemodialysis (HEMO) trial with oligoanuria (residual urine output <200 ml/d), key predictors of higher baseline serum sodium concentrations included having higher estimated dry weight, serum albumin, and serum creatinine levels (proxy of muscle mass), suggesting that nutritional status may be an important determinant of having normonatremia versus dysnatremia.⁸ In contrast, the strongest predictors of having lower serum sodium concentrations were receipt of higher ultrafiltration volumes, having underlying diabetes, and higher serum glucose levels. In an analysis of 11,555 prevalent hemodialysis patients across 12 countries from the Dialysis Outcomes and Practice Patterns Study (DOPPS) I and III cohorts, Hecking *et al.*⁵ similarly observed that proxies of favorable nutritional status such as higher body mass index, serum albumin, and serum creatinine levels were associated with higher serum sodium levels, whereas greater intradialytic weight loss was associated with lower sodium levels. Notably, there was also a positive association between residual kidney function (present in 42% of the cohort) and serum sodium levels. To further elucidate the interrelationships between hyponatremia, protein-energy wasting (as one of the most potent predictors of death in chronic kidney disease

and dialysis patients^{37,38}), and mortality, Dekker *et al.*⁴ examined 8883 hemodialysis patients from the MONITORING Dialysis Outcomes (MONDO) initiative who underwent nutritional and fluid status assessment by bioimpedance spectroscopy and ascertainment of inflammation using C-reactive protein levels. Logistic regression analyses showed that malnutrition (defined as lean tissue index <10th percentile of age- and sex-matched controls) and inflammation (defined as C-reactive protein >6.0 mg/l) were associated with higher likelihood of hyponatremia (sodium <135 mEq/l), whereas fluid overload (defined as overhydration >+1.1 liters) was associated with lower likelihood of hyponatremia. Data on residual kidney function and urine output were not reported in this study.

There has been mixed data with respect to dialysis treatment characteristics as predictors of serum sodium levels. Although ultrafiltration volume has been linked with hyponatremia,^{5,8} not all studies have not shown a consistent association between dialysate sodium concentration and serum sodium levels. In a cohort of DOPPS participants among whom 55%, 20%, and 25% of patients were prescribed dialysate sodium concentrations of 140 mEq/l, >140 mEq/l, and <140 mEq/l, respectively, the dialysate sodium concentration was not associated with serum sodium level.⁵ Similarly, in a cohort of prevalent hemodialysis patients from a large US dialysis organization among whom 48%, 13%, and 11% of patients received fixed dialysate sodium prescriptions of 140 mmol/l, >140 mmol/l, and <140 mmol/l, respectively, and 28% were prescribed sodium modeling/profiling regimens, mean predialysis serum sodium levels did not vary according to dialysate sodium concentrations.³⁹ However, further studies are needed to determine the optimal dialysis prescription approach that best aligns dialysate-serum sodium concentrations and favorably impacts serum sodium levels while avoiding interdialytic weight gain, thirst, and hypertension.

Peritoneal Dialysis

There have been comparatively fewer reports of clinical characteristics associated with hyponatremia in peritoneal dialysis patients. To address this knowledge gap, one recent study by Dimitriadis *et al.*¹¹ examined risk factors associated with incident hyponatremia among patients receiving care in a Toronto Home Peritoneal Dialysis Unit. Among 166 patients who underwent at least 2 consecutive serum sodium measurements separated by at least 1 month, and who had follow-up of at least 60 days, 15% of patients developed hyponatremia (defined as sodium <130 mmol/l on 2 consecutive measures) over the course of 1 year. In multivariable adjusted analyses, higher levels of residual kidney function were independently correlated

with higher serum sodium levels, whereas greater use of icodextrin was associated with lower sodium levels. Among a subcohort of 24 patients who developed hyponatremia, the investigators found that weight loss and a decline in serum potassium levels correlated with a decline in serum sodium, corroborating that poor nutritional status is a risk factor for incident hyponatremia in peritoneal dialysis patients. In a cross-sectional analysis of peritoneal dialysis patients from a large national dialysis organization in the United States, higher levels of residual kidney function (defined by renal urea clearance) and serum albumin levels (as an index of nutritional and inflammation status) had an inverse association with lower sodium levels (defined as <136 mEq/l).²

Hyponatremia and Mortality in Dialysis Patients Hemodialysis

A large body of data has shown that there is an inverse association between lower serum sodium levels and higher mortality risk in hemodialysis patients (Table 2).^{3,5–8,39–41} Among 11,555 prevalent hemodialysis patients across 12 countries from the DOPPS I and III cohorts, higher serum sodium levels (ascertained from the mean of patients' first 3 sodium measurements) examined in 4-mEq/l increments was associated with lower mortality risk.⁵ When examined as tertiles (categorized as <137, 137 to <140, and ≥140 mEq/l), sodium levels <137 mEq/l were independently associated with a 45% higher mortality risk in analyses that comprehensively accounted for confounders such as sociodemographics, comorbidities, laboratory tests, intradialytic weight loss, dialysate sodium concentrations, and residual kidney function. In a subsequent study of 8883 patients from 17 European countries in the international MONDO initiative (median dialysis vintage 3.6 years), baseline serum sodium levels <135 mEq/l were associated with a 65% to 70% higher death risk (reference: sodium ≥ 135 mEq/l) independent of protein-energy wasting indices and markers of fluid overload.⁴ With respect to incident hemodialysis patients who manifest distinct characteristics (i.e., greater residual kidney function yet higher mortality rates and less survivor bias) compared with prevalent patients, Nigwekar *et al.*⁶ examined 6127 patients who newly initiated hemodialysis from the Accelerated Mortality on Renal Replacement (ArMORR) cohort, and found that each 3-mEq/l decrement in baseline sodium level was associated with increasingly higher death risk. When examined as a categorical variable, serum sodium levels <135 mEq/l (reference: sodium ≥135 mEq/l) were associated with a 42% higher 1-year all-cause death risk and a 29% higher cardiovascular death risk. Although the

Table 2. Selected studies of association of serum sodium levels and mortality risk in hemodialysis (HD) and peritoneal dialysis (PD) patients

HD				
Author (year)	Cohort	Sodium definition	Outcome ^a	Analytic notes on multivariable adjustment
Waikar <i>et al.</i> (2011) ⁸	1549 prevalent HD patients (US – HEMO)	<ul style="list-style-type: none"> Baseline and time-varying sodium. Examined as continuous variable with 4-mEq/l increments. 	<ul style="list-style-type: none"> Baseline analyses <ul style="list-style-type: none"> > Each 4-mEq/l increment associated with 11% ↓ mortality risk. Time-varying analyses <ul style="list-style-type: none"> > Each 4-mEq/l increment associated with 9% ↓ mortality risk. 	<ul style="list-style-type: none"> Adjusted for nutritional status and diabetes. Not adjusted for RKF.
Hecking <i>et al.</i> (2012) ⁵	11,555 prevalent HD patients (12 countries – DOPPS I & III)	<ul style="list-style-type: none"> Mean of first 3 sodium measurements. Examined as continuous (1-mEq/l increments) and categorical variable (tertiles: <137, 137 to <140, ≥140 mEq/l). 	<ul style="list-style-type: none"> Continuous analyses <ul style="list-style-type: none"> > Each 1-mEq/l increment associated with 5% ↓ mortality risk. Categorical analyses <ul style="list-style-type: none"> > Lowest tertile associated with 45% ↑ mortality risk. 	<ul style="list-style-type: none"> Adjusted for nutritional status, diabetes, and RKF.
McCausland <i>et al.</i> (2012) ³⁹	2272 prevalent HD patients (US – Satellite)	<ul style="list-style-type: none"> Baseline sodium level. Examined as continuous variable with 4-mmol/l increments. Stratified by low versus high dialysate sodium concentration (<140 vs. ≥140 mmol/l). 	<ul style="list-style-type: none"> Low dialysate strata <ul style="list-style-type: none"> > Each 4-mmol/l increment associated with 28% ↓ mortality risk. High dialysate strata <ul style="list-style-type: none"> > Each 4-mmol/l increment associated with 14% ↓ mortality risk. 	<ul style="list-style-type: none"> Adjusted for nutritional status and diabetes. Not adjusted for RKF.
Sahin <i>et al.</i> (2012) ⁷	697 prevalent HD patients (Turkey)	<ul style="list-style-type: none"> Baseline sodium level. Examined as continuous (1-mmol/l increments) and categorical variable (quartiles). 	<ul style="list-style-type: none"> Continuous analyses <ul style="list-style-type: none"> > Each 1-mmol/l increment associated with 13% ↓ mortality risk. Categorical analyses <ul style="list-style-type: none"> > Lowest sodium quartile associated with 2.13-fold ↑ mortality risk. 	<ul style="list-style-type: none"> Adjusted for nutritional status and diabetes. Not adjusted for RKF.
Mandai <i>et al.</i> (2013) ⁴¹	332 prevalent HD patients (Japan)	<ul style="list-style-type: none"> Baseline sodium level. Examined as continuous (1-mEq/l increments) and categorical variable (tertiles: <138, 138–140, >140 mEq/l). 	<ul style="list-style-type: none"> Continuous analyses <ul style="list-style-type: none"> > Each 1-mEq/l increment associated with 9% ↓ mortality risk. Categorical analyses <ul style="list-style-type: none"> > No association with mortality. 	<ul style="list-style-type: none"> Adjusted for nutritional status and diabetes. Not adjusted for RKF.
Nigwekar <i>et al.</i> (2013) ⁶	6127 incident HD patients (US – ArMORR)	<ul style="list-style-type: none"> Baseline sodium <135 mEq/l. 	<ul style="list-style-type: none"> Sodium <135 mEq/l associated with 42% ↑ 1-year mortality. 	<ul style="list-style-type: none"> Adjusted for nutritional status and diabetes. Not adjusted for RKF.
Dekker <i>et al.</i> (2016) ⁴	8883 HD patients (Europe – MONDO)	<ul style="list-style-type: none"> Baseline sodium <135 mEq/l. 	<ul style="list-style-type: none"> Sodium <135 mEq/l associated with 65%–70% ↑ mortality. 	<ul style="list-style-type: none"> Adjusted for nutritional status and diabetes. Not adjusted for RKF.
Rhee <i>et al.</i> (2016) ³	27,180 incident HD patients (US – DaVita)	<ul style="list-style-type: none"> Baseline and time-varying sodium categories: <130, 130 to <132, 132 to <134, 134 to <136, 136 to <138, 138 to <140, 140 to <142, 140 to <144, ≥144 mEq/l. 	<ul style="list-style-type: none"> Baseline analyses <ul style="list-style-type: none"> > Sodium <138 mEq/l associated with ↑ mortality. > Sodium ≥144 mEq/l associated with ↓ mortality. Time-dependent analyses: <ul style="list-style-type: none"> > Sodium <138 mEq/l associated with ↑ mortality. > Sodium ≥144 mEq/l associated with ↑ mortality. 	<ul style="list-style-type: none"> Adjusted for nutritional status and diabetes. Not adjusted for RKF.
PD				
Author (year)	Cohort	Sodium definition	Outcome	Analytic notes on multivariable adjustment
Kang <i>et al.</i> (2013) ¹²	387 PD patients (Korea)	<ul style="list-style-type: none"> Baseline sodium <135 mmol/l. 	No association with mortality.	<ul style="list-style-type: none"> Adjusted for nutritional status and RKF. Not adjusted for diabetes nor icodextrin use.
Chen <i>et al.</i> (2014) ¹⁰	318 incident/prevalent PD patients (Taiwan)	<ul style="list-style-type: none"> Baseline sodium quartiles: 124–135, 136–139, 140–141, 142–148 mEq/l. 	No association with mortality.	<ul style="list-style-type: none"> Adjusted for nutritional status. Not adjusted for diabetes, RKF, nor icodextrin use.
Kim <i>et al.</i> (2015) ²²	441 incident PD patients (Korea)	<ul style="list-style-type: none"> Time-averaged sodium level. Examined as continuous (1-mEq/l increments) and categorical variable (tertiles: <137, 137 to <139, ≥139 mEq/l). 	<ul style="list-style-type: none"> Continuous analyses <ul style="list-style-type: none"> > Each 1-mEq/l increment associated with 10% ↓ incident CV events. Categorical analyses <ul style="list-style-type: none"> > Lowest tertile associated with 94% ↑ incident CV events. 	<ul style="list-style-type: none"> Adjusted for nutritional status, RKF, and icodextrin use. Not adjusted for diabetes.
Chang <i>et al.</i> (2014) ⁹	441 incident PD patients (Korea)	<ul style="list-style-type: none"> Time-averaged sodium level. Examined as continuous (1-mEq/l increments) and categorical variable (tertiles: <137, 137 to <139, ≥139 mEq/l). 	<ul style="list-style-type: none"> Continuous analyses <ul style="list-style-type: none"> > Each 1-mEq/l increment associated with 21% ↓ all-cause mortality and 23% ↓ infection-related mortality. Categorical analyses <ul style="list-style-type: none"> > Lowest tertile associated with 3.35-fold ↑ all-cause mortality and 3.18-fold ↑ infection-related mortality. 	<ul style="list-style-type: none"> Adjusted for nutritional status, RKF, and icodextrin use. Not adjusted for diabetes.

(Continued on next page)

Table 2. (Continued)

PD				
Author (year)	Cohort	Sodium definition	Outcome	Analytic notes on multivariable adjustment
Tseng <i>et al.</i> (2014) ¹³	99 PD patients admitted for peritonitis (China)	<ul style="list-style-type: none"> Sodium ≤ 130 mEq/l (2 occasions). 	<ul style="list-style-type: none"> Sodium ≤ 130 mEq/l 77-fold \uparrow in-hospital mortality. 	<ul style="list-style-type: none"> Not adjusted for nutritional status, diabetes, RKF, nor icodextrin use.
Al-Chidadi <i>et al.</i> (2016) ⁴³	3108 incident PD patients (UK)	<ul style="list-style-type: none"> Baseline sodium level. Examined as continuous (1-mEq/l increments) and categorical variable (tertiles: <138, 138 to <140, ≥ 140 mmol/l). 	<ul style="list-style-type: none"> Continuous analyses <ul style="list-style-type: none"> $>$ Each 1-mmol/l increment associated with 5% \downarrow mortality. Categorical analyses <ul style="list-style-type: none"> $>$ Lowest tertile associated with 49% \uparrow mortality. 	<ul style="list-style-type: none"> Adjusted for nutritional status and diabetes. Not adjusted for RKF nor icodextrin use.
Ravel <i>et al.</i> (2016) ²	4687 incident PD patients (US)	<ul style="list-style-type: none"> Baseline and time-varying sodium categories: <134, 134 to <136, 136 to <138, 138 to <140, 140 to <142, 140 to <144, ≥ 144 mEq/l. 	<ul style="list-style-type: none"> Baseline analyses <ul style="list-style-type: none"> $>$ Sodium <140 mEq/l associated with \uparrow mortality. Time-dependent analyses: <ul style="list-style-type: none"> $>$ Sodium <136 mEq/l associated with \uparrow mortality. 	<ul style="list-style-type: none"> Adjusted for nutritional status, diabetes, and RKF. Not adjusted for icodextrin use.

ArMORR, Accelerating Mortality on Renal Replacement; CV, cardiovascular; DOPPS, Dialysis Outcomes and Practice Patterns; HD, hemodialysis; HEMO, Hemodialysis; MONDO, MONitoring Dialysis Outcomes; PD, peritoneal dialysis; RKF, residual kidney function.

^aAll estimates presented from multivariable adjusted models.

Upward-pointing arrow = increased; downward-pointing arrow = decreased.

forementioned studies might suggest that lower serum sodium levels are harmful, while higher levels are protective, the lack of repeated measures data did not allow for assessment of longitudinal changes in serum sodium over time. Furthermore, the relatively narrow spectrum of serum sodium levels (i.e., exclusion of patients with serum sodium >145 mEq/l in the latter study⁶) may have precluded granular assessment of serum sodium levels at higher ranges. In a study of 1549 prevalent hemodialysis patients from the HEMO trial with longitudinal laboratory data, predialysis serum sodium levels were examined as a continuous variable.⁸ Analyses of baseline and time-varying sodium showed that each 4-mEq/l sodium increment was associated with a 9% to 11% lower death risk. However, it should be noted that examination of sodium as a continuous variable in 4-mEq/l increments (i.e., as opposed to a categorical variable or spline) precluded detection of nonlinear associations of sodium and death risk. To address these limitations, Rhee *et al.*³ evaluated both baseline and time-varying sodium levels granularly categorized into 9 groups among 27,180 incident US hemodialysis patients in the largest study of dysnatremia and mortality in dialysis patients to date. Using conventional Cox regression models that comprehensively adjusted for confounders such as interdialytic weight gain, comorbidities, and nutritional status, analyses of baseline sodium (as a proxy of long-term sodium-mortality associations⁴⁰) demonstrated an inverse linear association between serum sodium and mortality, such that sodium levels <138 mEq/l were incrementally associated with higher mortality, whereas levels ≥ 144 mEq/l were associated with lower mortality risk (Figure 2a). In contrast, analyses of time-dependent sodium (as a proxy of short-term sodium-mortality associations⁴⁰) demonstrated a

U-shaped relationship, such that sodium levels <138 mEq/l and ≥ 144 mEq/l were associated with higher death risk (Figure 2b). Recent data from the MONDO initiative have also shown that higher levels of sodium variability across all predialysis serum sodium levels were associated with higher mortality risk, highlighting the need for future studies examining variability as a clinical predictor of adverse outcomes.⁴²

Peritoneal Dialysis

Although existing studies of dysnatremia and mortality in peritoneal dialysis patients have been conducted in comparatively smaller-sized cohorts, many but not all have shown a potent association between lower serum sodium and higher death risk in this population (Table 2).^{2,9,10,12,13,22,43} Among the positive studies, Chang *et al.*⁹ first examined the association between time-averaged sodium levels categorized as tertiles (<138 , 137 to <139 , ≥ 139 mEq/l) with mortality in a prospective study of 441 incident peritoneal dialysis patients from Korea. The investigators found that sodium levels <137 mEq/l were associated with higher all-cause and infection-related mortality risk. In a subsequent rigorous study, Al-Chidadi *et al.*⁴³ examined 3108 incident peritoneal dialysis patients from the UK Renal Registry who underwent sodium measurement at a single-point-in-time 90 days after treatment initiation. Upon examining sodium levels categorized into tertiles (<138 , 138 to <140 , ≥ 140 mmol/l), the investigators also found that lower sodium levels <138 mmol/l were associated with higher death risk. When sodium-mortality associations were examined across age strata, associations between the lowest sodium tertile with death persisted in the youngest age group (ages 18–54 years) only. In the largest study of sodium and outcomes conducted among peritoneal dialysis patients to date, Ravel *et al.*²

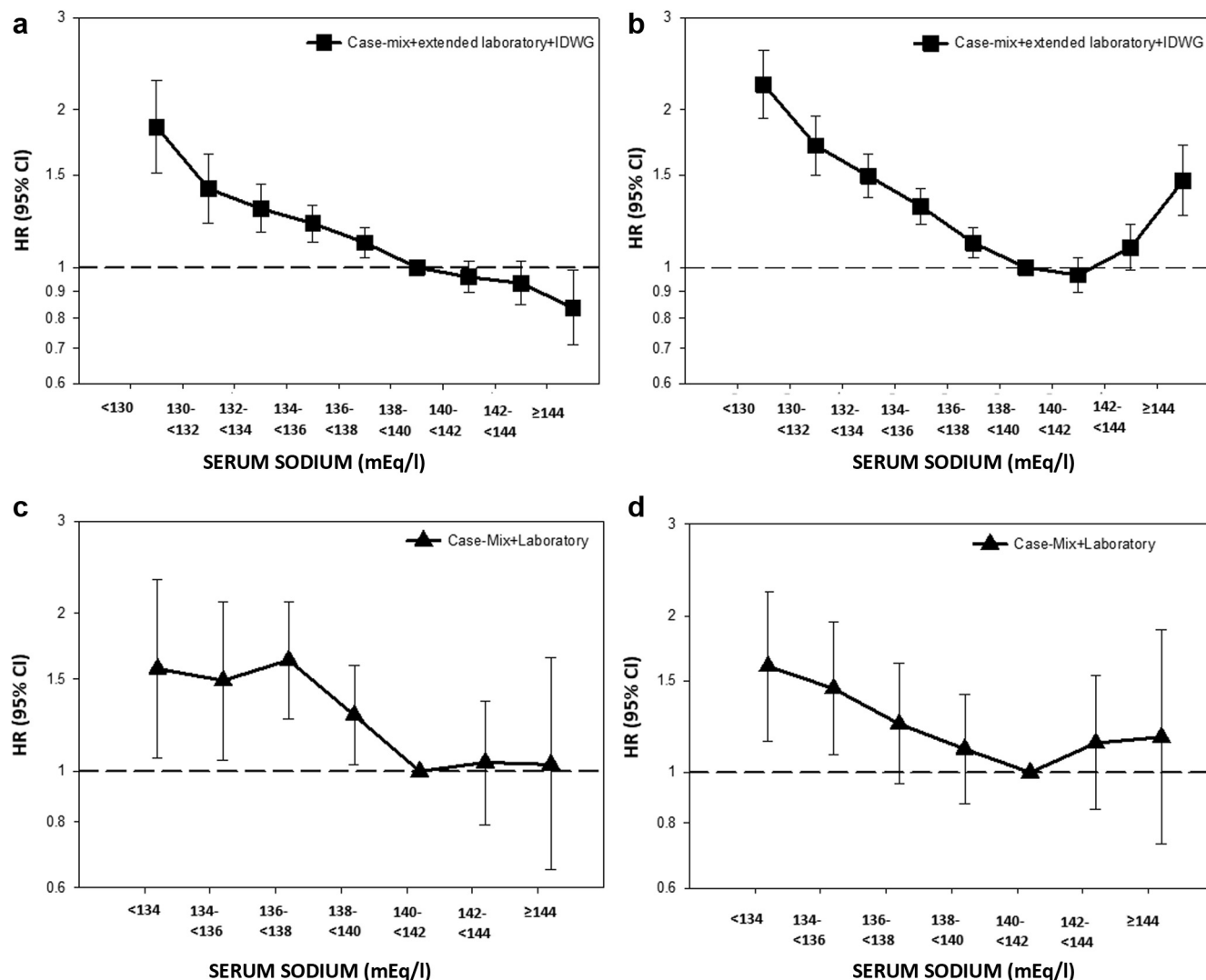


Figure 2. Association of baseline (a) and time-varying (b) serum sodium levels and mortality in hemodialysis patients. Association of baseline (c) and time-varying (d) serum sodium levels and mortality in peritoneal dialysis patients. CI, confidence interval; HR, hazard ratio; IDWG, interdialytic weight gain. Adapted from Ravel *et al.*² and Rhee *et al.*³

examined 4687 incident peritoneal dialysis patients from a large dialysis organization who had availability of both baseline and longitudinal sodium measurements. Assessment of fine gradations of baseline sodium showed that levels <140 mEq/l were associated with higher death risk independent of case-mix and laboratory covariates (Figure 2c), whereas time-varying analyses showed that sodium levels <136 mEq/l were associated with incrementally higher mortality risk (Figure 2d). These findings may suggest that the impact of lower sodium levels on long-term and short-term mortality in peritoneal dialysis patients may exist at different thresholds.⁴

Potential Mechanisms Underlying Hyponatremia and Mortality

It remains uncertain as to whether the hyponatremia-mortality associations in dialysis patients are causal, or due to confounding by conditions that predispose to

low serum sodium levels (e.g., interdialytic weight gain and volume overload; low solute intake and protein-energy wasting; underlying comorbidities; Figure 3a). However, there are several potential pathways by which lower serum sodium levels may directly lead to higher mortality risk (Figure 4).

Central Nervous System Toxicity

Hyponatremia may promote injury to the central nervous system by engendering cerebral edema, herniation, encephalopathy, seizures, and coma.^{15–17} Even mild reductions in sodium may lead to disequilibrium, gait instability, and falls and subsequent fractures.^{1,44–47} For example, in a study of 476 incident and prevalent peritoneal dialysis patients recruited from 5 treatment centers in China by Xu *et al.*,⁴⁸ cross-sectional analyses of serum sodium with 3 cognitive tests were examined, including the (i) Modified Mini-Mental State Examination to ascertain global cognition, (ii) Trail making

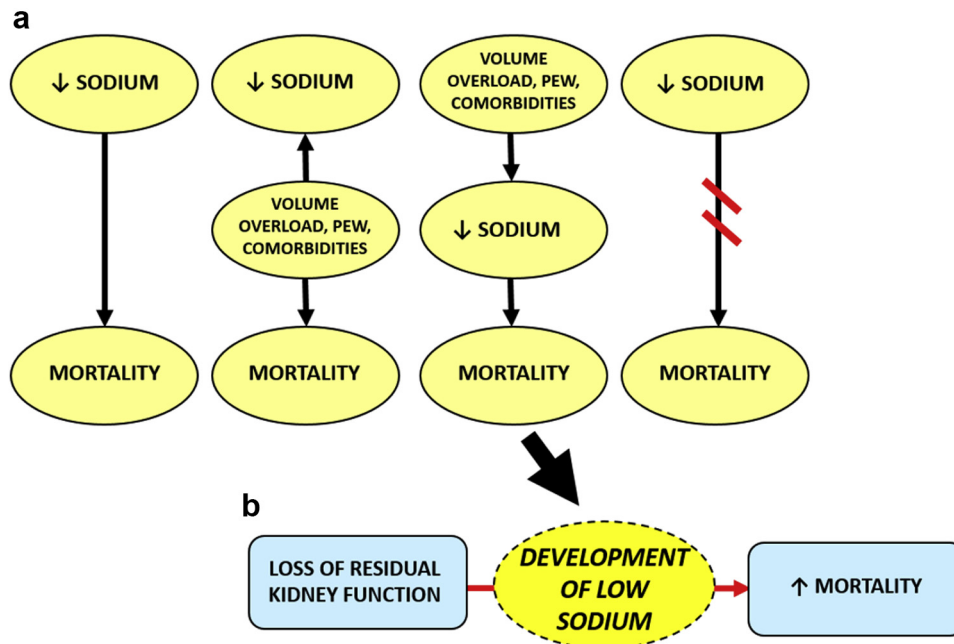


Figure 3. Varying scenarios of the interrelationship between serum sodium and mortality in dialysis patients (a). Low serum sodium as a mechanistic link between loss of residual kidney function and higher mortality risk (b). Upward-pointing arrow = increased; downward-pointing arrow = decreased. PEW, protein-energy wasting.

tests A and B to assess executive function, and (iii) Repeatable Battery for the Assessment of Neuropsychological Status to measure immediate and delayed memory and language ability. It was found that serum sodium levels ≤ 135 mmol/l were associated with worse global cognition and executive function.

Fracture Risk

In addition to causing disequilibrium and gait abnormalities, hyponatremia may further augment risk of

fracture via reduction of bone mineral density and volume.^{49,50} Experimental models have demonstrated that hyponatremia activates osteoclasts, manifesting higher calcium and suppressed parathyroid hormone levels.^{6,50,51} It has also been suggested that lower sodium levels directly stimulate osteoblasts, leading to increased alkaline phosphate levels. Indeed, in a cross-sectional analysis of incident hemodialysis patients from the ArMORR cohort, hyponatremia was associated with hypercalcemia, hypoparathyroidism, and

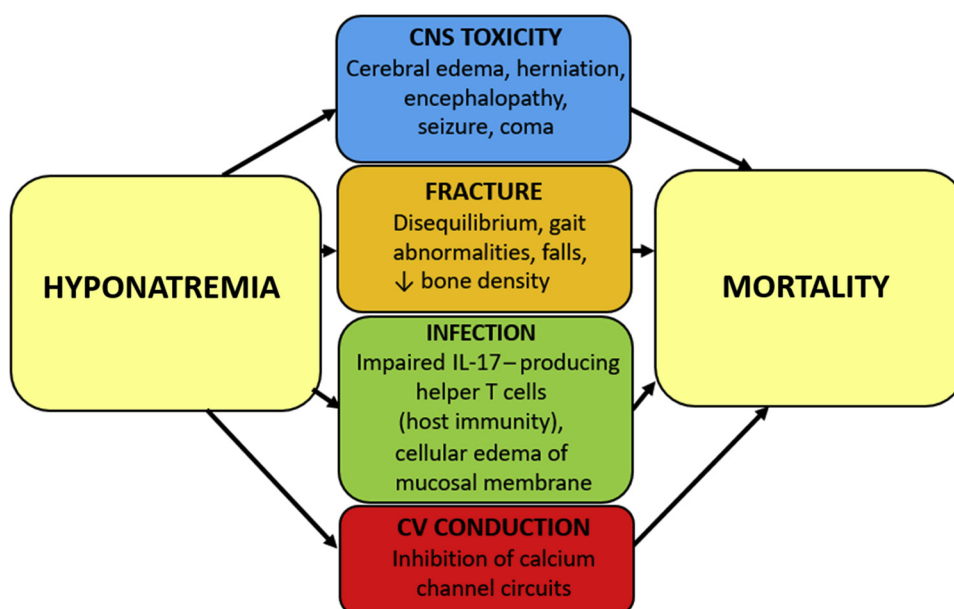


Figure 4. Potential mechanisms underlying the relationship between hyponatremia and mortality. Downward-pointing arrow = decreased. CNS, central nervous system; CV, cardiovascular; IL, interleukin.

elevated alkaline phosphatase levels.⁶ These findings were corroborated by a study of US incident/prevalent peritoneal dialysis patients which showed that higher parathyroid hormone levels were associated with a lower likelihood of having a low sodium defined as <136 mEq/l (i.e., positive association between parathyroid hormone and sodium levels).² Finally, in a study of elderly patients >60 years of age from a health maintenance organization with 2 or more sodium measurements, those with prolonged chronic hyponatremia, defined as having a sodium of <135 mmol/l for more than 90 days, had a 4.5-fold higher risk of hip fracture compared with normonatremic patients.¹⁸ Risk was even higher (i.e., 7.6-fold higher risk) among patients with moderate hyponatremia, defined as sodium levels <130 mmol/l.

Immune Dysfunction and Infection

Emerging data also indicate that hyponatremia may be a risk factor for infection due to impaired function of interleukin-17 producing helper T-cells that play a key role in host immunity and breakdown of microbial barrier function due to cellular edema or mucosal membranes.^{14,19–21,41} In a study of 332 prevalent hemodialysis patients from Japan, incrementally lower serum sodium tertiles (derived from 3 monthly sodium measurements) were associated with increasingly higher infection-related hospitalization risk.⁴¹ In another retrospective analysis of 99 peritoneal dialysis patients in China admitted for peritonitis, 27% of patients were found to have sodium levels of <130 mEq/l based on 2 consecutive measurements from the first 2 days of their hospitalization, among whom there was a higher frequency of gram-negative bacilli infection.¹³

Cardiovascular Complications

Finally, hyponatremia may also contribute to adverse cardiovascular outcomes vis-à-vis inhibition of calcium channel circuits in the heart leading to impaired cardiac function.²³ These findings bear particular importance to dialysis patients in whom cardiovascular disease and infection are the 2 most common causes of death.⁵² Indeed, in a study of 441 incident peritoneal dialysis patients whose baseline serum sodium levels were categorized as tertiles (<137 , 137 to <139 , ≥ 139 mEq/l), those in the lowest tertile had a higher risk of a new-onset fatal or nonfatal cardiovascular events, defined as coronary artery disease (ascertained by receipt of angioplasty or coronary artery bypass graft surgery, or sustaining a myocardial infarction/angina), congestive heart failure, cerebrovascular disease, or peripheral artery disease (defined as receipt of revascularization or amputation).²² Further rigorous studies including clinical trials are needed to determine whether correction of dysnatremia is associated with improved

outcomes in dialysis patients, as well as the optimal sodium target in this population.

Hyponatremia as a Link Between Loss of Residual Kidney Function and Mortality

A large body of evidence has demonstrated that preservation of residual kidney function and urine output is associated with greater survival in both peritoneal dialysis and hemodialysis patients, whereas a decline in these parameters over time is associated with incrementally higher death risk.^{53–57} Furthermore, in peritoneal dialysis patients, the attenuation in their early survival advantage over time has been attributed to loss of residual kidney function. Indeed, given its continuous nature, residual kidney function offers considerable benefits with respect to volume control, solute clearance, and uremic toxin removal even among patients receiving dialysis.^{58,59} As several epidemiologic studies have shown that the loss of residual kidney function is characterized by transition from normal to low sodium levels,¹¹ it has been posited that hyponatremia may be a mechanistic link between decline in residual kidney function and mortality risk (Figure 3b). Further studies of the interplay between residual kidney function and sodium balance, as well as the causal implications upon survival in dialysis patients are needed.

Prevention and Management of Hyponatremia in Dialysis Patients

Given limited data addressing management of dysnatremia in dialysis patients, based on case report data, expert opinion, and extrapolation of observations from the nondialysis population, in the rare occasion in which a hemodialysis or peritoneal dialysis patient is hyponatremic and symptomatic (i.e., hyponatremic encephalopathy), we would support treatment similar to that of patients with normal kidney function, namely administration of 3% hypertonic saline.^{19,60} Although further rigorous study of optimal dysnatremic management approaches in patients with end-stage renal disease are needed, there has been a published report of a hemodialysis patient with severe symptomatic hyponatremia (serum sodium 98 mEq/l) treated with i.v. hypertonic saline and immediate hemodialysis with a standard bath afterward, with subsequent improvement in mental status.⁶¹ However, appropriate precautions should be taken when using this intervention. For example, it is extremely important to use hypertonic saline cautiously to avoid potential complications, including assessment of fluid overload, particularly among patients who are anuric, and ensuring there is adequate access to dialysis if required. In this regard, we recommend providing a 100-ml bolus of 3% hypertonic saline, which will mitigate risk of overaggressive correction and can conveniently be administered via peripheral i.v. route.^{19,60,62} It

is also important to highlight that other pharmacotherapies that are used in hyponatremia such as vasopressin receptor antagonists (e.g., vaptans) do not have a role in dialysis patients. Among patients with chronic and/or recurrent asymptomatic hyponatremia, prevention and correction of free water excess is a cornerstone of management. Patients should first be counseled to avoid excess free water intake relative to the amount removed with dialysis. Among hemodialysis patients, if free water overload cannot be controlled with conventional thrice-weekly treatment, we recommend short daily hemodialysis, which has been shown to be effective in controlling fluid status and electrolyte abnormalities (i.e., phosphorus), while maintaining predialysis serum sodium levels within normal range.^{63,64}

In peritoneal dialysis patients, hyponatremia is more commonly observed and may also be confounded by the high prevalence of diabetes and uncontrolled hyperglycemia in this population. Although management of hyponatremia in peritoneal dialysis may be more challenging for these reasons, modification of the dialysis prescription to augment fluid removal is also recommended. Dextrose-based solutions may also be used in lieu of icodextrin given their preferential aquaporin-mediated removal of water versus sodium²⁵; however, this approach should be accompanied by careful attention to and adequate control of glycemic status, given the potential risks of (i) hyperglycemia-induced dilutional hyponatremia,²⁴ as well as (ii) elevated glucose levels driving increased thirst and free water consumption. In both peritoneal dialysis and hemodialysis patients with residual kidney function, loop diuretics can also be prescribed to augment free water excretion.

Given the high prevalence of malnutrition in dialysis patients and its associations with dysnatremia^{4,8,11} and mortality,³⁷ nutritional status should also be prioritized. Although there are compelling data in support of fluid restriction in dialysis patients,^{65–68} there is a paucity of evidence demonstrating the benefits of dietary sodium restriction in this population,⁶⁹ and further study of the latter's effects on clinical outcomes (e.g., including fluid status, survival, hospitalization, and patient's perceptions of thirst) is needed. Although we do not recommend complete relaxation of dietary recommendations, the restriction of fluid and dietary sodium intake should be reserved for patients with adequate nutritional status, and excess dietary limitations that could potentially compromise energy and protein intake in this population should be avoided.^{69–71} Finally, among both hemodialysis and peritoneal dialysis patients, preservation of residual kidney function should be optimized in preventing the development of hyponatremia.^{11,24,25}

Future Directions and Conclusion

There has been considerable progress in our understanding of serum sodium derangements in the dialysis population. Multiple population-based studies have demonstrated a substantially higher prevalence of dysnatremia in both hemodialysis and peritoneal dialysis patients,^{2,3,5–13,40,48} and have also identified several shared risk factors for hyponatremia across these 2 modalities, including poor nutritional status^{5,8,40} and loss of residual kidney function.^{2,4} Across multiple studies of dialysis patients, lower serum sodium levels even in the normal range have been associated with adverse outcomes, including higher risk of all-cause mortality,^{2–9,13,39,41,43} cardiovascular events,²² infection-related complications,^{13,41} and cognitive deficits.⁴⁸ However, many areas of uncertainty remain, including (i) mechanistic pathways by which lower serum sodium levels are linked with higher mortality in dialysis patients, (ii) whether hyponatremia contributes to the heightened mortality associated with loss of residual kidney function, (iii) the impact of correction or prevention of sodium derangements through proper dietary intake (e.g., fluid <1 liter/d and sodium intake <3 g/d⁷⁰) and dialytic interventions (i.e., altered ultrafiltration, dialysate sodium concentrations) on outcomes, (iv) the optimal sodium target and degree of variability in this population, and (v) the impact of sociodemographic factors (e.g., race/ethnicity⁷²) on hyponatremia-outcome associations and implications in pediatric^{73,74} versus adult dialysis patients. Given the disproportionate prevalence and high mortality risk of dialysis patients, there is compelling need for further studies of the optimal management of sodium derangements in this population.

DISCLOSURE

All the authors declared no competing interests.

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